



Direct C-3 lithiation of 1-(triisopropylsilyl)indole

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Abstract—1-(Triisopropylsilyl)indole can be directly lithiated at 3-position with *tert*-BuLi-TMEDA in hexane at 0°C for 3 h. The generated lithio species is reacted with a variety of electrophiles to give 3-substituted 1-(triisopropylsilyl)indoles in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Functionalization of the indole ring at the 3-position has been effected generally by electrophilic substitutions or by reactions of indole *N*-Grignard reagents.¹ Highly reactive *N*-protected 3-lithioindoles are also important intermediates for the syntheses of 3-substituted indoles. The C-3 lithio species have been generated most satisfactorily by halogen–lithium exchange of the *N*-protected 3-halogenoindoles. The first example of this reaction was reported by Saulnier and Gribble in 1982.^{2a} They generated 1-(benzenesulfonyl)-3-lithioidole by treatment of the corresponding 3-iodo (or bromo) indole with *tert*-BuLi at –100°C region.² Although a number of common electrophiles can be readily introduced at the 3-position in good yields at the same temperature, a problem is the tendency of 1-(benzenesulfonyl)-3-lithioidole to rearrange to the more stable 2-lithio species at higher temperatures. In order to overcome this problem, Bosch et al. employed bulky and non-coordinating *N*-silyl protecting groups.³ They reported, for example, 1-(*tert*-butyldimethylsilyl)-3-lithioindole, generated from the corresponding 3-bromoindole at –78°C, is stable even upon warming to room temperature.

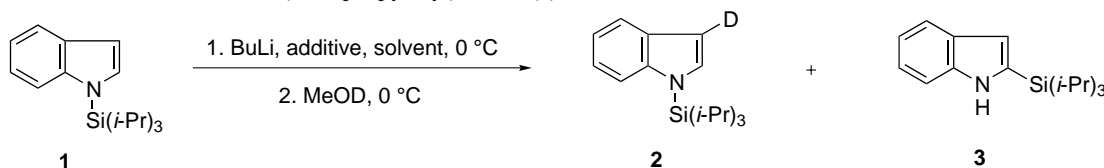
The direct and selective C-3 lithiation of simple *N*-protected indoles, on the other hand, has been neglected for a long time.⁴ This is apparently because the competitive C-2 lithiation is expected to be much more facile under the reaction conditions.⁵ In 1993, however, Klingebiel et al. reported that 1-(di-*tert*-butylfluorosilyl)indole could be lithiated at C-3 by *tert*-BuLi at room temperature.⁶ Recently, we investigated regioselective lithiation of bulky *N*-acyl indoles⁷ and discov-

ered that 1-(2,2-diethylbutanoyl)indole could be lithiated at 3-position selectively by using *sec*-BuLi-PMDTA (*N,N,N',N',N''*-pentamethyldiethylenetriamine) at –78°C.^{7b} These results suggested that if the indole nitrogen was protected by an appropriate bulky substituent to prevent preferential C-2 lithiation, the selective lithiation at 3-position was feasible. Based upon this assumption, we investigated the direct C-3 lithiation of readily prepared 1-(triisopropylsilyl)indole (**1**)⁸ to establish a convenient and general route to 3-substituted indoles.

The conditions for selective C-3 lithiation of **1** were explored by the deuteration experiments (Table 1). At first, we tested *sec*-BuLi-PMDTA as a lithiating agent, which was successfully employed for the selective C-3 lithiation of 1-(2,2-diethylbutanoyl)indole^{7b} (entry 1). The reaction was carried out at 0°C for 1 h in diethyl ether followed by quenching with MeOD. After chromatography, the substrate (**1**+**2**) was isolated in 91% yield. The deuterium incorporation at C-3 was estimated to be 29% by ¹H NMR analysis.⁹ In this reaction, a small amount of 2-(triisopropylsilyl)indole (**3**) was also isolated. This compound must be formed by C-2 lithiation of **1** followed by N to C migration of triisopropylsilyl group.¹⁰ Next, we used *sec*-BuLi-*tert*-BuOK system in the same solvent (entry 2). To our surprise, the substrate was recovered only in 41% yield and the compound **3** was isolated in 49% yield. Deuterium was not incorporated at C-3 in the recovered substrate. This means the lithiation under these conditions was C-2-selective.¹¹ In entry 3, we examined *tert*-BuLi-TMEDA as a base in diethyl ether. The results were similar to those obtained in entry 1. The poor deuterium incorporation at C-3 under the conditions of entries 1 and 3 might be accounted for by rapid consumption of *sec*- or *tert*-BuLi by the solvent, at 0°C

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Table 1. Lithiation–deuteration of 1-(triisopropylsilyl)indole (**1**)^a

Entry	Base (equiv.)	Additive (equiv.)	Solvent	Time (h)	2+1 (%) ^b	<i>d</i> -content at C-3 (%) ^c	3 (%) ^b
1	<i>sec</i> - (3.0)	PMDTA (4.5)	Et ₂ O	1	91	29	1
2	<i>sec</i> - (3.0)	<i>tert</i> -BuOK (4.5)	Et ₂ O	1	41	0	49
3	<i>tert</i> - (3.0)	TMEDA (4.5)	Et ₂ O	1	97	36	1
4	<i>tert</i> - (3.0)	TMEDA (4.5)	Hexane	1	92	53	3
5	<i>tert</i> - (3.0)	TMEDA (4.5)	Hexane	3	88	89	9
6	<i>tert</i> - (1.5)	TMEDA (1.8)	Hexane	3	93	93	3
7	<i>tert</i> - (1.5)	None	Hexane	3	99	0	0

^a Substrate **1**: solvent=0.4 mmol:5 mL (entries 1–5), 1.0 mmol:5 mL (entries 6, 7).

^b Isolated yield after column chromatography.

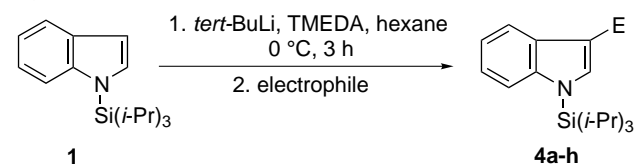
^c Deuterium content was estimated by ¹H NMR analysis, see: Ref. 9.

region.¹² Therefore, we decided to use hexane as a solvent hereafter. When lithiation was carried out with *tert*-BuLi-TMEDA in hexane at 0°C for 1 or 3 h, the deuterium incorporation, in fact, was greatly improved (entries 4, 5). Under the optimized conditions [*tert*-BuLi (1.5 equiv.), TMEDA (1.8 equiv.), hexane, 0°C, 3 h], the substrate was recovered in 93% yield and the deuterium incorporation at C-3 was 93% (entry 6). TMEDA was indispensable for the success of this reaction (entry 7).

Using the lithiation conditions thus established, we carried out 3-selective functionalizations of **1** using a range of common electrophiles. The results were summarized in Table 2. In the reaction with MeI, inseparable mixture of the 3-methylated product **4a** (83%) and

the starting material **1** (11%) was obtained after chromatography (entry 1). In the reactions with other electrophiles, however, the pure 3-substituted products **4b–h** were readily isolated by column chromatography in good yields (entries 2–8). It is noteworthy that 2-functionalized products derived from 1-triisopropylsilyl-2-lithioindole were never isolated, though a small amount (2–3%) of 2-(triisopropylsilyl)indole was formed in every case. These results indicated 1-(triisopropylsilyl)-2-lithioindole was thermally unstable and rearranged rapidly to the more stable 2-(triisopropylsilyl)-1-lithioindole under the lithiation conditions.¹⁰

In conclusion, we have developed a procedure for direct C-3 lithiation of indole ring using 1-(triisopropylsilyl)indole (**1**) as a substrate. This method is apparently more useful than a conventional halogen–lithium exchange protocol,^{2,3} because it is not necessary to synthesize intermediate 3-halogenoindoles and also because the lithiation can be conducted at convenient ice-bath temperature. The ready availability of **1** and high yields of 3-substituted products **4a–h** clearly indicated the superiority of triisopropylsilyl protecting group over di-*tert*-butylfluorosilyl⁶ and 2,2-diethylbutanoyl⁷ protecting groups for direct C-3 lithiation of indole. Since *N*-triisopropylsilyl group is readily removed by TBAF,^{3,8,13} the method developed herein is highly useful for the synthesis of a wide range of 3-substituted indoles.

Table 2. Selective C-3 functionalization of 1-(triisopropylsilyl)indole (**1**)^a

Entry	Electrophile	Product	E	Yield (%) ^b
1	MeI	4a	Me	83 ^c
2	TMSCl	4b	TMS	84
3	BrF ₂ CCBrF ₂	4c	Br	92
4	DMF	4d	CHO	78
5	CO ₂	4e	CO ₂ H	88
6	ClCO ₂ Et	4f	CO ₂ Et	69
7	ClCONEt ₂	4g	CONEt ₂	78
8	<i>tert</i> -BuNCO	4h	CONHBu- <i>tert</i>	73

^a For typical experimental procedure, see: Ref. 14.

^b Isolated yield unless otherwise noted.

^c The yield of **4a** was extrapolated from the inseparable mixture of **4a** and **1** by ¹H NMR analysis.

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9. ¹H NMR spectrum of **1** (CDCl₃, 400 MHz): δ 1.14 (d, *J*=7.7 Hz, 18H), 1.70 (sept, *J*=7.7 Hz, 3H), 6.62 (dd, *J*=1.1 and 3.3 Hz, 1H), 7.10 (dt, *J*=1.5 and 7.3 Hz, 1H), 7.13 (dt, *J*=1.5 and 7.3 Hz, 1H), 7.37 (d, *J*=3.3 Hz, 1H), 7.51 (d, *J*=7.3 Hz, 1H), 7.62 (d, *J*=7.3 Hz, 1H). Deuterium incorporation at C-3 was estimated by integration of an absorption of H-3 using that of H-7 as the reference. The signals at δ 6.62 and δ 7.51 were assigned to be H-3 and H-7 protons, respectively by the NOE experiments.
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